SPECIAL ARTICLES

What Does It Mean to Be a Cancer Gene Carrier? Problems in Establishing Causality From the Molecular Genetics of Cancer

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This article addresses the following question: What does it mean to be a cancer gene carrier? The existence of families prone to cancer has prompted an intense search for predisposing heritable gene mutations. Genes that impart susceptibility to colorectal, breast, and ovarian cancers have been recently identified. It is doubtful, however, that the action of a single mutant gene totally accounts for the development of malignant disease. The mutant gene likely causes cancer in these family members only in conjunction with other genes, environmental factors, or both. Furthermore, although an individual carrier of a mutant gene within a cancer-prone family has an increased risk of malignancy, nutritional, pharmacologic, or other interventions may still confer protection. Extrapolations from cancer-prone families to the general population are even more problematic. The excess risk of malignancy among carriers of mutant genes who are not members of cancer-prone families is unknown. Large-scale epidemiologic studies are needed to determine the magnitude (or even the existence) of such excess risk. [J Natl Cancer Inst 87:1126-1130, 1995]

That some families suffer from an extraordinarily high incidence of colon, breast, ovarian, or other cancers is well documented (*1,2*). The existence of these families has propelled an intense search for predisposing heritable gene mutations. Building on the results of linkage studies (*3,4*), investigators have reported two mutant genes, MSH2 on chromosome arm 2p (*5,6*) and MLH1 on chromosome arm 3p (*7,8*), for hereditary nonpolyposis colon cancer (HNPCC) (*9*). Two additional DNA-mismatch repair genes, PMS1 on chromosome 2q and PMS2 on chromosome 7p, have also been implicated in HNPCC (*10*). Recently, the breast cancer and ovarian cancer susceptibility gene BRCA1 was identified on chromosome 17q (*11,12*). In addition, a second breast cancer-susceptibility gene, BRCA2, has been localized to chromosome 13q12-13 (*13*). BRCA2 appears to confer an elevated risk of breast cancer but not ovarian cancer. The identification of mutant genes for other tumors may not be far behind (*2*). Once a heritable cancer gene has been cloned and sequenced, it becomes possible to identify its (potentially myriad) mutant forms. Identification of these specific mutations opens the possibility of developing and implementing genetic tests for cancer predisposition (*14*).

An implicit assumption is that the heritable mutant gene causes the cancer. Caution is warranted in making such an assumption, however, as suggested by the emerging complexities underlying cystic fibrosis, an autosomal recessive disorder (*15,16*). More than 400 mutations of the cystic fibrosis gene have been identified to date (*17*). This large number of mutations makes the development of a gene mutation test particularly problematic, although in some populations it may be possible to screen for the 10-20 most common mutations that comprise 90%-95% of all cystic fibrosis gene mutations (*17*). Of particular note are observations that a number of individuals who have been found to carry two mutant alleles that are thought to engender cystic fibrosis have minimal signs of clinical disease (*18-21*). The causal connections involved in the pathogenesis of cystic fibrosis appear not to be totally reducible to the action of a single mutant gene.

There is no a priori reason to believe that the situation for cancer should be any less complicated. In this article, we examine the causal inferences appropriately drawn from current developments in the molecular genetics of cancer. In particular, we will address the question: What does it mean to be a cancer gene carrier?

What Can We Reasonably Infer From Cancer-Prone Families?

Let us assume that extensive investigations of a set of cancer-prone families have culminated in the successful identification

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of a gene for a given cancer site. We assume further that all mutations have been identified. Finally, for presentation purposes, we make the simple assumption that a single germline mutation of this gene (MUTGENE1) is associated with cancer in these families.

Table 1, based on a hypothetical study of cancer-prone families, illustrates the strong relationship between MUTGENE1 and cancer. In the cancer-prone families, a very large proportion of those affected with the cancer carry MUTGENE1; a very large proportion of those unaffected do not carry MUTGENE1. In other words, MUTGENE1 can be said to cosegregate strongly with the cancer. This cosegregation could be quantified in traditional epidemiologic terms as a relative risk (RR), defined as $[a/(a + b)]/[c/(c + d)]$ (*22*). (RR = 19 in Table 1, where a = MUTGENE1 positive and disease positive, b = MUTGENE1 positive and disease negative, c = MUTGENE1 negative and disease positive, and d = MUTGENE1 negative and disease negative.) One can also say that there is nearly full penetrance (*23*); a very high proportion of gene carriers ($a/[a + b]$ = 95% in Table 1) is ultimately affected. This proportion is analogous to the screening parameter—positive predictive value—that is, the proportion of those with a positive test who also have the disease (*24*).

Given the high degree of cosegregation and penetrance indicated in Table 1, what causal inferences can we appropriately draw regarding the relationship between MUTGENE1 and cancer?

Table 1. Hypothetical relation between MUTGENE1 and cancer within a cancer-prone family

		Affected +	Affected −
MUTGENE1	+	95 [a]	5 [b]
	−	5 [c]	95 [d]

Inference 1:
MUTGENE1——> Cancer

This inference implies that MUTGENE1 is a necessary and sufficient cause of cancer within these families. It should be noted that even when MUTGENE1 is necessary and sufficient for the development of a hereditary cancer, penetrance could be somewhat less than 100% because of misclassification of the cancer or to competing causes of death within these families (*23*). Moreover, nonhereditary or sporadic malignancies, reflecting another causal pathway, may occasionally occur.

One can plausibly infer, however, three other causal pathways consistent with Table 1. In each of these inferences MUTGENE1 is necessary but not sufficient to cause cancer.

Inference 2:
MUTGENE1 + GENE2 ——> Cancer

MUTGENE1 produces malignant tumors only in the presence of one or more other genes (either a mutant gene or a polymorphic locus in which one or more alleles increases risk). In other words, there is a biologic interaction between MUTGENE1 and GENE2 with respect to the genesis of malignant tumors.

What role might GENE2 play? At a cellular level, it might act with MUTGENE1 in some cell-regulatory process or, alternatively, it might influence the metabolic activation of a procarcinogen. At the level of gross pathology, GENE2 could influence the initial development of a malignancy, the age of onset, or the number of tumors.

Min/Mom genes in mice represent a potential example of this multigene interaction (*25*). The mouse with multiple intestinal neoplasia (Min) carries a mutant adenomatous polyposis coli (APC) gene and develops many intestinal adenomas, making the Min mouse a potentially valuable model of familial large-bowel cancer. Mom-1 (modifier of Min-1 gene) strongly modifies the tumor number in Min-positive animals (that is, those with one copy of the Min mutation). It is possible, though still only speculative, that a human homologue of Mom-1 exists and influences the number of tumors in patients with APC or Gardner's syndrome. It is also possible that Min/Mom-like genes exist for other organ systems.

Inference 3:
MUTGENE1 + ENVIRONMENTAL FACTOR ——> Cancer

MUTGENE1 leads to malignancies only in the presence of one or more environmental factors (gene–environment interaction) (*23*).

Phenylketonuria (PKU) illustrates the role of gene–environment interaction in the etiology of disease (*26*). Mutations at the phenylalanine hydroxylase (PAH) locus produce defects in the PAH system that interfere with the conversion of phenylalanine to tyrosine, causing, in turn, an accumulation of toxic phenylpyruvic acid and other abnormal metabolites. This sequence of biochemical events is expressed clinically by mental retardation; peculiarities of gait, stance, and sitting posture; a "mousy" odor; light pigmentation; eczema; and epilepsy. The clinical syndrome is expressed, however, only in the presence of a phenylalanine-containing diet in the early years of life. The sequelae are substantially reduced or not expressed if a low-phenylalanine diet is consumed early in life.

A potential cancer-related example of this inference is cutaneous malignancy among persons with xeroderma pigmentosum. Skin cancer occurs at both a very high rate and an early age among individuals with xeroderma pigmentosum, an inherited autosomal-recessive DNA repair-deficient disorder with marked clinical and laboratory hypersensitivity to UV radiation (*27*). Sunlight exposure appears to play an important role in the induction of these cutaneous cancers. Although it is unknown whether sunlight or other UV radiation exposure is necessary for the development of skin cancer in persons with xeroderma pigmentosum, anecdotal observations suggest that lifelong avoidance of sunlight exposure substantially reduces the incidence of cutaneous malignancy in xeroderma pigmentosum-affected individuals.

Inference 4:
MUTGENE1 + GENE2 + ENVIRONMENTAL FACTOR ——> Cancer

In this inference, mutant MUTGENE1 causes cancer only if it acts in conjunction with one or more additional genes and one or more environmental factors. One can imagine fairly complicated scenarios involving multiple genes and environmental factors. For example, one study (*28*) of genetic susceptibility in smoking-related lung cancers has shown an increased risk of lung cancer among individuals with both a homozygous rare allele of the cytochrome p450IA1 gene and homozygous deletion of the Mu-class glutathione *S*-transferase gene (GST1).

As indicated by Table 1, we have assumed that MUTGENE1 cosegregates strongly with cancer in these families. How can we account for this observation if MUTGENE1 is a necessary but not sufficient cause, as in inferences 2 through 4? One possibility is that virtually all family members carry GENE2, have been exposed to ENVIRONMENTAL FACTOR, or both. That is, GENE2 and ENVIRONMENTAL FACTOR are background characteristics of all family members. Although evidence supporting a causal role for MUTGENE1 would clearly emerge from linkage studies in this situation, linkage data would not reveal the causal contribution of GENE2 and ENVIRONMENTAL FACTOR.

Genetic Heterogeneity

Although genetic heterogeneity does not bear directly on our primary question of what happens to a gene carrier, we note for the sake of completeness that, for some familial cancers, MUTGENE1 may be a sufficient but not necessary cause (Fig. 1). In Fig. 1, both MUTGENE1 and GENE2 operate independently (and sufficiently) through independent pathways. However, inferences 2 through 4 could pertain to each mutant gene pathway. Recent findings support the existence of this genetic heterogeneity for both HNPCC [MSH2 on chromosome arm 2p (*5,6*), MLH1 on 3p (*7,8*), PMS1 on 2q, and PMS2 on 7p (*10*)] and breast cancer [BRCA1 on chromosome 17q (*11,12*) and BRCA2 on 13q (*13*)]. Note that under these conditions of genetic heterogeneity, the proportion of cancer deriving from the GENE2 ——> cancer pathway may be substantially greater than that from the MUTGENE1 ——> cancer pathway.

Conclusions to Be Drawn From Strong Gene-Cancer Cosegregation Within Families

First, the gene mutation does substantially increase risk, even if the precise causal pathways are not clear. It may be that MUTGENE1 operates in conjunction with another heritable gene or with an environmental factor, but the fact remains that an individual is at increased risk of developing cancer if he or she carries MUTGENE1 and is a member of a cancer-prone family.

Second, intervention involving the elimination (or, in some cases, the addition) of an environmental factor may still be valuable. Adoption of a low-phenylalanine diet is clearly useful in preventing children with PKU from developing severe neurologic damage. It may be that changes in diet are of value even among those carrying the gene(s) for HNPCC; that is, the gene(s) may be operative only in the face of chronic consumption of certain foods and nutrients. Similarly, alterations of some lifestyle factors may reduce the likelihood of developing breast or ovarian cancers in those women carrying the gene(s) for these malignancies.

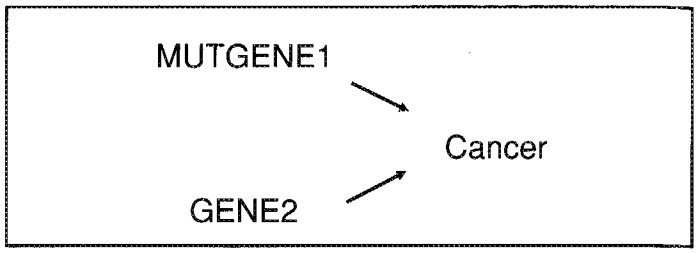

Fig. 1. Schematic diagram of genetic heterogeneity, whereby two genes operate through independent pathways to cause cancer.

What Can We Infer About Gene Carriers in the Population?

What does it mean to be a MUTGENE1 carrier but not a member of a cancer-prone family? We now refer to the same set of four inferences from the cancer-prone family findings. In the context of the general population, however, we do not assume strong cosegregation and full penetrance for MUTGENE1 and cancer.

How can we determine in the general population whether MUTGENE1 is a necessary and sufficient cause of cancer (inference 1) or whether one of the alternative inferences 2 through 4 is applicable? That is, what is the risk of cancer for a MUTGENE1 carrier in the general population?

An Epidemiologic Approach to Evaluating the Risk of Being a Gene Carrier

One approach to answering this question is to conduct a population-based observational epidemiologic study. Table 2 presents a 2 × 2 contingency table that reflects the results of a cohort or case–control study of the relationship of mutant MUTGENE1 carrier status to the incidence of cancer. Standard epidemiologic measures of association can be used here: RR, $(a/a + b)/(c/c + d)$, for a cohort study and odds ratio (OR), ad/bc (an estimate of RR), in a case–control investigation. Results from such studies can tell us whether, in fact, there is an increased risk of cancer among MUTGENE1 carriers relative to noncarriers.

Table 2. Generalized 2 × 2 contingency table reflecting results of epidemiologic study of relation between MUTGENE1 and cancer in the population

		Cancer	
		+	–
MUTGENE1	+	a	b
	–	c	d

The epidemiologic studies needed to estimate the cancer risk among MUTGENE1 carriers may be independently conducted or may be carried out within existing cohort and case–control investigations or ongoing clinical trials. We recognize that a number of ethical and legal issues, including those bearing on notification policy, need to be resolved before gene testing can be integrated in ongoing studies. Although critical, these issues are beyond the scope of this article.

Sample size requirements for such epidemiologic studies depend on the incidence of the cancer, the minimum RR one wishes to detect, and, in particular, the prevalence of MUTGENE1 in the general population. Little information is available on the prevalence of mutant genes such as APC, MSH2, MLH1, BRCA1, and BRCA2. Table 3, which is based on standard sample size tables for epidemiologic studies (*29*), presents the sample size required to detect small, moderate, and large RRs for a range of prevalences of MUTGENE1. The range of prevalences in Table 3 corresponds with what other investigators have estimated for some common malignancies; the upper bound for the OR in Table 3 (OR = 10) is consistent with (or even more conservative than) what has been observed in genetic epidemiologic studies (*9,23,30,31*). As Table 3 indicates, epidemiologic studies of the risk conferred by MUTGENE1-carrier status are indeed feasible. With, for example, a prevalence of 0.005 in the general population (as reflected in the control group), a case–control study of 300 cases with an equal number of controls would have a 90% power to detect an OR of 10. More than 2100 cases and the same number of controls, however, would be required to detect an OR of 3.

If MUTGENE1 were a necessary and sufficient cause of cancer, we would expect the RR from our epidemiologic study to be extremely high. (It should be infinite, but error in assessment of MUTGENE1 carrier status or cancer assessment could make the RR finite, though still extremely large.) If the RR is elevated, but not extremely so, then one of the following three conditions applies. 1) One of the alternative inferences 2 through 4 is true. That is, MUTGENE1 is not a sufficient cause (though, as inferences 2 through 4 indicate, it may be a necessary one). 2) MUTGENE1 is a sufficient cause, but it is not the only one (and therefore is not necessary). In other words, genetic heterogeneity, reflected in Fig. 1, is at work. 3) Classic confounding is operative. That is, the prevalence of a true cancer-causing factor is greater among mutant gene carriers than among noncarriers. Such confounding is potentially assessable by standard epidemiologic analytic techniques (*22*).

Table 3. Sample size estimates (No. of cases needed) for a case–control study of MUTGENE1-carrier status vs. cancer*

	Proportion of controls carrying mutant MUTGENE1 (mutation prevalence)				
OR†	0.001	0.005	0.01	0.05	0.1
1.5	105 265	21 174	10 668	2261	1219
3.0	10 489	2127	1076	237	133
10.0	1435	293	150	37	23

*Assumes two-sided $\alpha = .05$.
†The odds ratio (OR) is an estimate of relative risk (RR).

Need for Caution in Extrapolating From Families to Populations

One point is critical. The fact that there is a very strong association between MUTGENE1 positivity and cancer incidence within families does not necessarily translate into a strong association between positive carrier status and cancer in the general population. In other words, an 87% likelihood that a BRCA1 carrier born into one of the (rare) breast cancer (only)-prone families will develop breast cancer over her lifetime (*32*) does not mean that a BRCA1 carrier from the general population has anywhere near that lifetime risk.

This potential discordance in the strength of gene–disease relationships in families compared with populations can be explained as follows. Inferences 2 through 4 are plausible explanations for strong MUTGENE1–cancer cosegregation within families if, as we discussed above, all or most family members carry GENE2, have been exposed to environmental factors, or both. MUTGENE1 carriers in the general population arguably are considerably less likely than cancer-prone family members to carry GENE2 or to have been exposed to environmental factors. Because MUTGENE1 is not in itself sufficient to cause cancer, many MUTGENE1 carriers in the general population will not develop cancer. Therefore, the risk of cancer for MUTGENE1 carriers versus noncarriers may be only modestly elevated—or perhaps elevated hardly at all. Furthermore, we can conclude that population testing for MUTGENE1 (with a less than extremely high RR) will tell us little about an individual's fate. For a BRCA1 carrier, an excess cancer risk of, for example, 100% (i.e., RR = 2.0) is in the same range of risk associated with standard breast cancer risk factors such as late age at birth of first child (*33*). One cannot determine whether a woman carrying the gene will or will not get breast cancer any more than one could be certain about the fate of a woman who had her first child at (for example) age 36 years. The most that could be done would be to add this piece of information (being a gene carrier) into an overall breast cancer risk profile. Of course, if the RR for being a BRCA1 carrier is 50, then the lifetime breast cancer risk for a carrier is considerably greater than that for a noncarrier—and the risk may dwarf that conferred by traditional reproductive risk factors. We would still, however, be dealing only in probabilities and could not be certain of an individual carrier's breast cancer future.

Using Gene-Carrier Status to Enhance the Search for Environmental Causes

As has been pointed out by other investigators (*34*), the identification of a gene associated with cancer, even if it is not a sufficient cause, can help in the search for environmental causes. If a gene acts in concert with an environmental factor (inference 3, for example), it is informative to confine observational—and even intervention—studies to those who are gene carriers or, alternatively, to stratify analysis on gene-carrier status. This approach will tend to sharpen RRs (or augment intervention effects) and thereby increase the power to detect important (and potentially modifiable or avoidable) environmental risk factors. Without knowledge of gene-carrier status in this context, RRs

for environmental factors tend to be diluted by the inclusion of noncarriers who cannot get cancer (at least through this gene-based pathway).

Conclusion

We conclude with two summary points. 1) Even within cancer-prone families, inferences about gene–cancer relationships can be complex. Interventions targeted to environmental risk factors may still be relevant. 2) Before the findings from studies of cancer-prone families can be extrapolated to the general population, explicit observational epidemiologic studies of gene–cancer relationships need to be conducted. It behooves all who wish to make the most of the advances in molecular genetics to plan now for conducting such studies.

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Notes

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